REMARKS

This response is to the Final Office Action dated October 7, 2005. Claims 1-19 are pending and are rejected. The submission of a terminal disclaimer to overcome a nonstatutory double patenting rejection for claims 1-7, 11, and 12, is submitted herewith.

In a phone interview on February 23, 2005 with the Examiner, the representative for the Applicant enunciated the claimed invention as a method where a superoxygenated composition is applied to the surface of a tissue such that with sufficient contact time the partial pressure of oxygen in tissue below that surface cells, subepithelial, increases by 30 to 120% above baseline levels. As found in the specification, the superoxygenated composition is defined as a pharmaceutically acceptible vehicle which contains oxygen microbubbles. See page 6 ln 12-18, page 7 ln 22-29, page 10 ln 6-12, page 11 ln 6-26. A preferred superoxygenated composition is specifically stated in dependent claim 13. The use of any specific bubble stabilizing agent is not claimed, disclosed or suggested in the instant application. The superoxygenated compositions have O_2 concentrations of about 45 to about 220 ppm, as found in the specification and recited in dependent claim 10. See page 5 ln 23-24. Applicant respectfully requests that the Examiner consider the following arguments and reconsider the rejection.

In the Final Office Action the Examiner concluded that claims 1-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lundgren et al. (US 6,127,428) in view of Ladin et al. (US 5,792,090) further in view of Kolta et al (US 6,139,876).

Applicants request reconsideration and respectfully traverse the position that the present invention was obvious to one of ordinary skill in the art over Lundgren et al (Patent '428) entitled "Method of Enhancing Transport of Gases to Tissues" in view of Ladin (Patent '090) entitled "Oxygen Generating Wound Dressing" and further in view of Kolta et al. (Patent '876) entitled "Gel with Increased Oxygen Content". The present invention entitled "Method of Increasing Tissue Oxygenation" is directed to significantly increasing the partial pressure of oxygen in the damaged tissue, 30 to 120% above baseline. Oxygenation of the tissue by this composition can occur because the O_2 is present in a vehicle such as water as a microbubble of a sufficiently small size to promote the diffusion of O_2 into tissue such as skin. The O_2 microbubble

containing composition can be applied to a surface in a manner that is in direct contact with air, open system. The method of the present invention differs significantly from that of the cited art in composition, manner of use, and efficacy to an extent that is not obvious from the cited art.

The cited art does not recite a method employing an equivalent superoxygenated composition. The cited art does not teach the ability to achieve the large increase in subepithelial O_2 because of applying a composition of the present invention. Applicants respectfully submit that the demonstration of the promoted healing by a gel that had been stored at a high pressure of O_2 in Kolta (Patent '876) with the perfluorocarbon microbubbles in Lundgren ('428) with the extra-body treatment of an oxygen generating source in Ladin ('090) was not obvious and much of that taught in the cited references teaches away from the present invention. Kolta (Patent('876) disclosed that O_2 was not a significant factor in healing. Lundgren ('428) taught the need of a perfluorocarbon to optimally stabilize a microbubble that was not designed to or demonstrated to directly deliver O_2 to tissue nor that the use of microbubbles could significantly increased the ppO_2 in tissue. Ladin ('090) does not demonstrate the diffusion of O_2 through skin or any other cellular matter to increase the subepithelial ppO_2 and teaches one of ordinary skill in the art not to expect an increase of O_2 levels below the surface by the application of the disclosed method. The three cited inventions are addressed separately below.

About Ludgren (Patent '428), the Examiner stated:

Lundgren et al (Patent '428) disclose a method for increasing partial pressure of oxygen in tissues or organ by perfusion or agitation in medical situations or conditions such as myocardial ischemia (abstract, col 3, lin 60; col 4, lin 30-35; col 8, lin 15-34; col 16, lin 20-30 and col 21, lin 1-5). According to Lundgren et al, an increase in partial pressure of at least 5% over controls is achieved (col 21, lin 1-5 and table 3 at col 19). The method disclosed in Patent '428 achieves an increase in partial pressure of oxygen in tissues using microbubbles stabilized in protein coating and having size of about 3-6 microns (col col 10, lin 65 and col 7, lin 45-50) with oxygen entrapped therein (col 4, lin 45-60 and col 7, lin 55-65).

Lundgren (Patent '428) does not specifically disclose the use of the method for increasing partial pressure of oxygen in the or skin of humans in which there is a wound or burn or ulcer.

Ludgren (Patent '428) teaches transporting gases through the circulatory system, a closed system, via perfluorocarbon microbubbles. The microbubbles contain perfluorocarbon and exchange gases, for example O_2 and CO_2, in the blood stream and are very different from the superoxygenated composition of the present invention which does not contain a perfluorocarbon. The perfluorocarbon is necessary to the method described by Lundgren (Patent '428) as it stabilizes the microbubble and permits the exchange of gases without the loss of the microbubble structure and keeps the microbubbles contained in the circulatory system. The perfluorocarbon microbubbles were designed to persist for up to several hours in the bloodstream. See col. 6 ln 35-39. These perfluorocarbon microbubbles stabilize the gas bubble permitting differences in the pressures within the bloodstream to promote diffusion of gases across the perfluorocarbon microbubble/blood interface. See col 7 ln 25-34. The perfluorocarbon microbubbles are not capable of, nor were they intended for, O_2 release without the exchange with another gas such as CO_2. Hence, the microbubbles of Lundgren (Patent '428) are designed to specifically store oxygen to the blood so that upon stopping the circulation of blood through the vessels supplying that tissue, oxygen remains available for some period of time to the blood until the perfluorocarbon microbubbles are completely exchanged, and this is a very different intended oxygenating mode to that of the present invention and cannot be used in the mode of the present invention where O_2 is delivered without exchange in the microbubbles.

Lundgren (Patent '428) only teaches stabilized microbubbles and indicates that alternately stabilized microbubbles, such as protein coatings, are inferior to the perfluorocarbon microbubbles, stating "because the stabilized free gas microbubbles derive stability from a mechanism other than a surface coating which may act to some degree as a permeability barrier, the microbubbles have been found useful for **optimal** (emphasis added) transport of gases." (col 4 ln 4-8) Since Lundgren (Patent '428) teaches that the microbubbles for transport are at optimal levels and that the microbubbles need a perfluorocarbon to achieve this optimal level and that alternate surface coatings will act as a permeability barrier, they can not motivate one to develop the perfluorocarbon free or other stabilizer free superoxygenated composition of the present

invention with any expectation of achieving the high levels of ppO_2 of 30 to 120% above baseline. Again, the superoxygenated composition of the present invention do not contain perfluorocarbons or other stabilizing agents and achieve much higher levels of subepithelial oxygenation, perhaps because of the absence of such stabilizers.

The level of O_2 in the air is approximately 160 mmHg at sea level, the level of O_2 in the arterial blood is approximately 81 mmHg and the level of O_2 in the arterial blood with the perfluorocarbon microbubbles while breathing a gas that is approximately 530 mmHg is approximately 420 mmHg. See Lundgren (Patent '428) col 19 Table 3 row headed PaO_2 mmHg. In contrast the superoxygenated compositions of the present invention are up to about 220 ppm or approximately 0.17 mmHg. The superoxygenated composition, where the vehicle is water, as in claim 13 of the present invention, a level of O_2 of 220 ppm would be approximately 1,500% of the maximum dissolvable O_2 at 0°C, and it is in respect to normally dissolved O_2 in vehicles such as water that the compositions are considered superoxygenated. If the only factor for oxygenating of tissue is the level of O_2 in the medium around the tissue, the superoxygenated compositions of the present invention would be inferior at oxygenating tissue to the perfluorocarbon microbubbles of Lundgren (Patent '428) and even inferior to that of air. This is not the case as disclosed in the instant application and the superior oxygenating ability of these superoxygenated compositions is a surprising result that is not obvious from the teachings of the perfluorocarbon microbubble of Lundgren (Patent '428). It is not obvious how reducing the proportion of O_2 in the composition bathing the tissue would increase the amount that is delivered into the tissue without some effect of the state of the superoxygenated composition.

Turning to the teaching of Lundgren (Patent '428) with respect to the extent of oxygenation one might expect, Lundgren (Patent '428) discloses a partial pressure of O_2 in many lines of the patent with many specific lines pointed out by the Examiner. However, most of these lines do not claim the partial pressure as an increased partial pressure and generally refer to the partial pressure of the O_2 in the microbubble or in the bloodstream and not to the partial pressure of O_2 in tissues or organ. The significant exception being col 21 lin 5 that refers to entries in Table 3 for $PmO_2(p)$ and PmO_2 defined as the partial pressure of O_2 in muscles measured with a platinum needle electrode and the partial pressure of O_2 in muscles with a

sensor, respectively. Furthermore, Lundgren (Patent '428) does not teach an increase of the ppO_2 due to the microbubbles when carefully considering the data disclosed. The following three paragraphs will analyze that data with some detail.

Lundgren (Patent '428) discloses the manners in which $PmO_2(p)$ and PmO_2 measurements for Table 3 were taken in col 17 lin 65 through col 18 lin 11. $PmO_2(p)$ was measured using a platinum electrode in the muscle while PmO_2 was measured using a sensor placed on the muscle through a 2 cm incision. Hence, $PmO_2(p)$ indicates any increase in the partial presure of O_2 in the tissue, but PmO_2 only indicates the partial presure of O_2 in a poorly circulating pool of blood in a cavity constructed on the surface of the tissue of interest (muscle). Row 11, headed $PmO_2(p)$, of Table 3 gives in column 1 the baseline partial pressure of O_2 in the muscle, where no O_2 other than that from air exchanging O_2 through the lungs via the blood. This is not the baseline to consider when judging the efficacy of the perfluorocarbon microbubbles in the oxygenation of the tissue. All of the measurements where a perfluorocarbon microbubble was used also had a second mode of increasing the ppO_2 in the tissue, which was increasing the O_2 content of the gas breathed into the lungs. For this reason the value in column 2 must be used as the baseline to asses the effect of using the perfluorocarbon microbubbles. Columns, 2 through 5, of Table 3 show statistically the same value for the partial pressure of O_2 in the muscle as all of the ranges overlap in a random fashion: 76-84 (col 2), 82-98 (col 3), 76-98 (col 4), and 74-98 (col 5). Hence, the inclusion of the perfluorocarbon microbubbles have not increased the ppO_2 in the muscle in a statistically significant manner. Again the perfluorocarbon microbubbles are employed for transport of gases rather than the direct oxygenation of tissue.

The PmO_2 values of Lundgren (Patent '428) col 9 Table 3 row 12 were measured using a sensor placed on the muscle in a relatively large, 2 cm, incision which would necessarily be bathed in blood containing the perfluorocarbon microbubbles. The values are for the partial pressure of O_2 at the surface of the sensor, not the partial pressure of O_2 in any tissue. Note, from Table 3 row 12, headed PmO_2, that the partial pressure of O_2 has increased significantly from column 1 to column 2 with a much greater increase than was observed for the partial pressure of O_2 in the muscle given in Table 3 row 11 columns 1 and 2-5. The increase shown in row 12 from column 1 to column 2 is what one of ordinary skill in the art would expect for the

increase of the partial pressure of O_2 in the blood, but not necessarily the tissue, by administering a breathing gas higher in O_2 content. This implies that the sensor is measuring the partial pressure of O_2 in the blood rather than in the tissue (muscle). The regular increase in the partial pressure of O_2 observed with time when perfluorocarbon microbubbles are included, as can be seen going from columns 3 through 5, further indicates that the sensor is not reading the partial pressure of O_2 in the tissue. This time dependent O_2 level should and would be questioned by anyone of ordinary skill in the art looking for motivation since all other values of Table 3 display a steady state value established before the first value disclosed at 5 minutes.

Perfluorocarbons have some of the lowest surface energies of all known materials and hence concentrate at surfaces, either solid-liquid, solid-gas (as at the sensor surface), liquid-liquid, or liquid-gas (as in the bloodstream stabilizing the microbubbles), to minimize the total energy of the system. Hence, in Lundgren (Patent '428) col 9 Table 3 row 12 columns 3 through 5, the kinetics of the growth of a sensor-oxygen containing perfluorocarbon microbubble interface is evident by the increase of the values of PmO_2 and these values have no relevance with respect to the partial pressure of O_2 **in** the muscle. This growing level of PmO_2 is in contrast to the values for $PmO_2(p)$ of row 11 of Table 3, which are for the partial pressure of O_2 **in** the muscle. The only reasonable interpretation of this data by one of ordinary skill in the art is that the perfluorocarbon microbubbles provide O_2 into the bloodstream, which pooled in a cut orifice, can then over time slowly diffuse and concentrate at the surface of the sensor, as is normal for perfluorocarbons. Other data for partial pressures of O_2, as PmO_2 in Tables 4, 5, and 6 (col 19-20) and Tables 9 and 10 (col 29 and 30, where PO_2R are determined using the method for PmO_2 in Table 3) do not give the time at which the readings in the blood on the muscle were taken after introduction of the perfluorocarbon microbubbles. Hence, it can not be concluded that one or ordinary skill in the art would be motivated to use microbubbles as taught in Lundgren (Patent '428) to increase oxygenation of tissue by the method of the present invention.

In summary, Lundgren (Patent '428) does not demonstrate a statistically significant increase the partial pressure of O_2 in tissue by the use of perfluorocarbon microbubbles, and does not suggest the direct diffusion of O_2 through skin or any other epithelial tissue. Rather, the data of Lundgren (Patent '428) permits one of ordinary skill in the art to conclude that

perfluorocarbon microbubbles were designed not to and do not diffuse significantly into tissue. Lundgren (Patent '428) could actually be considered to discourage the present invention as it suggests that the perfluorocarbon microbubbles are optimal for gas transport, yet can not achieve the superoxygenated levels of the present invention. Hence, Lundgren (Patent '428) does not obviate the use of microbubbles free of perfluorocarbon, for the direct diffusion of O_2 through tissue, and never demonstrates the achievement of a significant increase in the levels of ppO_2 in tissue attributable to the use of the microbubbles, or suggest any way to modify the perfluorocarbon microbubble system to achieve the tissue oxygenation of the present claimed invention.

With respect to Ladin (Patent '090) the Examiner stated:

Ladin et al (Patent '090) disclose a method of increasing the partial pressure or oxygenation of in human skin surface; e.g. wound infection caused by pathogens; burns; ulcers and scalds—abstract, col 4, lin 15-30; col 5, lin 25-30; and col 10, lin 20-50 and col 11, lin 35.

Neither Lundgren nor Laden disclosed the relationship between wound infection, wound healing, the increase in partial pressure of oxygen and the reasons or motivation for such application of a composition that can cause such increased tissue oxygenation.

Ladin (Patent '090) teaches the generation of O_2 at a wound surface in a closed, SARAN® wrap covered, system, but does not teach the formation of microbubbles. Applicant respectfully submit that Ladin (Patent '090) does not disclose a method to increase the partial pressure of O_2 in human skin only a wound dressing that generates O_2 at the surface of a wound. With respect to subepithelial O_2 enhancement, Ladin (Patent '090) only discloses the measured the partial pressure of O_2 on a probe inserted into the perichondrium that covers the cartilage of a rabbit's ear **after the skin and subcutaneous tissue was removed.** (col 10 ln 20-26 and Figs. 9a and 9b). Physically removing the skin to provide O_2 to the surfaces normally below the skin does not teach that O_2 can be delivered to that surface when the skin has not been removed. The wound dressing of Ladin (Patent '090) is intended *"to provide oxygen levels similar to those produced by moderate hyperbaric oxygen treatment"* (col 3 ln 17-20) where hyperbaric oxygen

treatment is stated to be a treatment where "*the relative oxygen concentration of the deep dermis (1.8-2.2 mm) is unchanged*" (col 1 ln 46-52). Hence, Ladin (Patent '090) teaches away from expecting a surface treatment to increase subepithelial levels of O_2 when treating skin.

The measured values shown for the partial pressure of O_2 measured in Ladin (Patent '090) are never disclosed to be the result of diffusion of O_2 through tissue and contrast significantly with the O_2 levels in tissue when compared to values in Lundgren (Patent '428). The measured data, considered in detail in the following two paragraphs, also highlights the specific shortcomings of Ladin (Patent '090) that was pointed to in the Background Art of the present application as a deficiency in the state of the art which necessitated the present invention. See page 3 ln 14-28 of the instant application. The wound dressing of Ladin (Patent '090) would necessarily supply hydrogen peroxide to a wound as is successfully avoided in the present invention. Again the present invention is for significant subepithelial increases in the ppO_2 by the administration of a superoxygenated composition of 45 to 220 ppm O_2 can not be considered obvious having knowledge of Ladin (Patent '090).

The value for the partial pressure of O_2, by a probe inserted into the perichondrium disclosed in Ladin (Patent '090) before the application of the wound dressing, of 100 mmHg is much higher than the value for the control in Lundgren (Patent '428) where no additional O_2 is supplied, ~56 mmHg, and is even higher than the partial pressure of O_2 measured in Lundgren (Patent '428) after the introduction of additional O_2 by breathing O_2 rich air with perfluorocarbon microbubbles present, ~86 mmHg. The value of Lundgren (Patent '428) with no additional O_2 supply but air is consistent with other values found in the literature for oxygenation of tissue by other means. The value of 100 mmHg in Ladin (Pat '090) is much higher than what has been observed in normal tissue. This suggests that the measured O_2 is not that in tissue and that the sensor may be in partial contact with air.

If one assumes no contact with air and that the values of Ladin (Patent '090) are for tissue and only require a calibration to bring them in line with Lundgren (Patent '428) and the general literature, the data in Ladin (Patent '090) is still not consistent with a process of increasing O_2 in tissue. Fig 9b of Ladin (Patent '090) shows that upon removal of the O_2 generating wound

dressing from atop the perichondrium, the partial pressure of O_2 at the oxygen measuring probe only returned to about 120 mmHg rather than the starting value of about 100 mmHg, in Fig. 9a, and remains at this higher level over the entire measurement period of approximately 8 minutes. These observations can not reflect the change of O_2 levels in tissue, as the level must continue to return to the initial baseline level rather than plateau at some higher level. However, the results are consistent with a O_2 containing hydrogen peroxide solution diffusing into the cavity around the oxygen measuring probe and the probe measured the partial pressure of O_2 in that solution. When the O_2 generating wound dressing was removed, after the free O_2 adjacent to the probe was lost from the cavity, over the period of approximately 1 minute in Fig. 9b, a steady state partial pressure of O_2 was established by the decomposition of hydrogen peroxide in the solution around the probe keeping the value higher than the initial baseline and essentially constant for the period of time until the experiment was stopped. Therefore, one of ordinary skill in the art would conclude that the apparent increase resulted from the diffusion of hydrogen peroxide and O_2 rich solution into the orifice around the oxygen measuring probe and does not reflect O_2 levels in the tissue. The avoidance of hydrogen peroxide on the wound is an achieved goal of the present invention. Therefore, Ladin (Patent '090) neither teaches that the O_2 generated at the surface defuses through tissue or is effective at oxygenating subepithelial tissue.

Effective diffusion of O_2 into or through tissue can not be concluded from the data presented in Ladin (Patent '090) by one of ordinary skill in the art, only that the wound dressing disclosed has the capacity of generating oxygen at the surface of the wound and bath the wound with hydrogen peroxide solution. One of ordinary skill in the art would not conclude that either Ladin (Patent '090) or Lundgren (Patent '428) suggest a method to increase the partial pressure of O_2 in mammalian tissue by administering a superoxygenated composition of the present invention. Hence, neither of these cited patents render obvious the method of the present invention that clearly demonstrates the increase of the partial pressure of O_2 in tissue by the use of a superoxygenated composition containing O_2 microbubbles. The Ladin (Patent '090) disclosure was made starting from a premise that subepithelial levels of O_2 would not increase, and provided no evidence that the method did increase subepithelial levels of O_2 to contradict this premise. Hence Ladin (Patent('090) teaches away from the present invention.

With respect to Kolta (Patent '876) the Examiner stated:

> Kolta et al (Patent '876) discloses would infection by aerobic bacteria and the effects of gelatin with oxygen contained therein on treatment (col 1, lin 30-45; col 2, lin 15-35). According to Kolta et al, the increased partial pressure of oxygen in the gel applied at the wound site facilitates healing of wound (col 3, lin 15-30; col 4, lin 60 and col 7, lin 1-5).
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> One of ordinary skill in the art would have been motivated to make a composition suitable for delivery of oxygen to a would site in order to increase partial pressure of oxygen at the wound or burn site such as disclosed by Lundgren et al where microbubbles have been used to increase tissue oxygenation of sites or organs. By applying such composition in the form of microbubbles or gel or lotion for delivery of oxygen to wound sites; one of ordinary skill would have expected to achieve increased tissue oxygenation and thereby facilitate the healing process at the wound or burn site as was achieved in the prior art (Patent '876, example 1 at col 6 and 7). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

The Examiner states that Kolta (Patent '876) discloses "the increased partial pressure of oxygen in the gel applied at the wound site facilitates healing". Applicants respectfully submit that this is not taught and that Kolta (Patent '876) only teaches a synergistic effect of gelatin treated with a high pressure of O_2, referred to as proloxin, provides an alternate mode of wound healing, demonstrated with burned skin. Kolta (Patent '876) rather than observing an increase in the rate of healing discloses that the formulation of the gel with a high pressure of O_2 only modifies the healing process promoted by the gelatin: "*The observation of the healing process demonstrated a uniform overall healing of the wound area treated by proloxin, while normal gelatin, although substantially facilitated the healing process itself, did not change the conventional character thereof to slowly proceed from the wound edges towards the central area. Hence, the difference lied between the uniform healing of the whole wound surface and the gradual healing directed from the outer zones to the central one.*" (col 7 lin 1-8) Rather than teaching that the increased partial pressure of oxygen in the gel applied to the wound site

facilitates healing of the wound as stated by the Examiner, Kolta (Patent '876) discloses: "*We have supposed that during the absorption of proloxin the oxygen supply alone does not support the process of creating new tissues to a sufficient extent*" (col 14 lin 1-3). Therefore Kolta ('876) cannot motivate the use of a composition which simply provides an O_2 supply free of some synergistic agent.

Furthermore, Kolta (Patent '876) discloses no evidence that O_2 is drawn into the tissue of the wound as the gelatin is absorbed. Kolta (Patent '876) states that the exposure of the gelatin stored with a high pressure of O_2 to the atmosphere results in a soft sputtering noise forming an opaque appearance to the gelatin. see col 4 ln 39-46 This means that the O_2 has escaped before application to a wound with the exception of what is dissolved, necessarily a much lower undefined value, and included in large, not micro-, bubbles, which was responsible for the opaque appearance and would certainly exchange O_2 with air many orders of magnitude faster than a gas could diffuse through a membrane such as skin. Claim 6 of Kolta (Patent '876) does not state that O_2 is drawn into the wound with the gelatin and nothing in the specification defines the stated microbubbles as being microbubbles in the sense and size of the present invention. The opaque appearance of the gel upon exposure to air implies that the bubbles in Kolta (Patent '876) are not of the small dimensions of the present invention, as would be obvious to one of ordinary skill in the art. As described in col 4 ln 46-66, the only measurements of O_2 content in the gel after removal from the pressurized container was done in a manner that cannot reflect the pressure after the gel liquefies on the skin since the pressures 0.2 and 0.49 MPa (2 and 4.8 atmospheres) that are recited are not physically possible for gas in a liquid of the sort described in equilibrium with the air, since the maximum pressure of even pure O_2 under these conditions cannot exceed 1 atmosphere or 0.1 MPa. The disclosure where an attempt to keep O_2 in the gelatin by spraying a layer of Plastubol over the gelatin to inhibit spontaneous O_2 release (col 6 Experiment 1) neither measured the O_2 content to determine that this was a successful encapsulation, nor is a parallel control experiment disclosed where no Plastubol was used such an assessment of that condition by a difference in result could be made.

As claimed in the instant application, a superoxygenated composition must be applied to a tissue for a sufficient period of time to achieve an increase in the ppO_2. Kolta (Patent '876)

could not possibly achieve a threshold level of time as disclosed in Experiment 1 col 6 and 7. The gelatin that was stored with a high pressure of O_2 was applied to the wound twice a day. Each application was apparently, although not well described, a 2.5% gelatin solution in water that liquefies at body temperature and therefore as a liquid could not be sufficiently thick to be considered a long lived O_2 supply. This method of application is consistent with the statement in Kolta (Patent '876) about the O_2 supply alone being insufficient to support the process of creating new tissue (col 14 lin 1-3)

It is possible that another condition of the gel treated with a high pressure of O_2 promotes the uniform healing of the wound and this appears to be the reason for reciting the synergistic effect of formulating the gelatin with a high pressure of O_2 in Kolta (Patent '876). For example, an alternate explanation might be that a pre-metabolism of the gelatin, an oxidation process that was disclosed to be needed for healing in Kolta (Patent '876), occurs to some extent in the package due to extremely high pressures of O_2 to yield metabolites that are drawn with the gelatin into the tissue and it was these metabolites that promoted the uniform healing of the wound. see col 14 lin 1-53.

Presumption of a mechanism based on the recited components of a composition should not be a substitute for considering only the definitive teaching of a reference. Therefore, one of ordinary skill in the art would conclude that Kolta (Patent '876) only teaches that a gel that has been treated with high O_2 pressure, 1.5 to 59 times normal atmospheric pressure, and rapidly looses O_2 when exposed to air and spread while liquefying over a wound, promotes uniform healing of a wound. Kolta (Patent '876) concludes that O_2 alone, contrary to the present invention, does not support the process of creating new tissue to a sufficient extent. Therefore Kolta (Patent '876) can be considered to teach that O_2 provides an undefined synergistic effect for a gelatin that was treated with O_2 and does not teach, as in the present invention, that the treatment of injured skin by a superoxygenated composition can increase the ppO_2 in the skin.

It is incorrect to conclude obviousness based on Lundgren (Patent '428) in view of Ladin (Patent '090) and further in view of Kolta (Patent '876). Lundgren (Patent '428) and Ladin (Patent '090) do not demonstrate and cannot achieve, although inferred to be optimized, the

significant increase in ppO_2 in tissue of the present invention and therefore would not motivate the use of a superoxygenated composition toward wound treatment. Lundgren (Patent '876) teaches that to have microbubbles a stabilizer must be included which teaches away from the present invention. Ladin (Patent '090) discloses the premise that subepithelial tissue cannot be elevated by the application of the O_2 generating wound dressing and never presents data or claims to the contrary, hence teaches away from the present invention. Kolta (Patent '876) teaches the healing of a wound by a gel where the gel was previously exposed to high O_2 pressures, but teaches away from the invention indicating that O_2 alone is insufficient to promote healing, and therefore does not provide motivation for a composition that does not contain a synergistic gelatin or other synergistic agent. Applicant respectfully requests that the Examiner withdraw the rejection of all claims, as the present invention could not have been obvious to one of ordinary skill in the art at the time the invention was made.

Applicants have made every effort to present claims that distinguish over the cited art, and it is believed that all claims are in condition for allowance. However, Applicants invite the Examiner to call the undersigned if it is believed that a telephonic interview (direct line (561) 671-3656) would expedite the prosecution of the application to an allowance. A fee for extension for response within two month is believed to be due, the Commissioner for Patents is hereby authorized to charge any deficiency in fees due or credit an excess in fees with the filing of the papers submitted herein during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
AKERMAN SENTERFITT

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